(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 May 2002 (23.05.2002)

PCT

(10) International Publication Number
WO 02/40033 A1

(51) International Patent Classification[7]: A61K 31/662, 9/107, A61P 17/16

(21) International Application Number: PCT/AU01/01475

(22) International Filing Date:
14 November 2001 (14.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/247,997 14 November 2000 (14.11.2000) US
PR 5499 6 June 2001 (06.06.2001) AU

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/40033 A1

(54) Title: FORMULATION CONTAINING PHOSPHATE DERIVATIVES OF ELECTRON TRANSFER AGENTS

(57) Abstract: There is provided an emulsion composition for therapeutic administration comprising: (a) at least one mono-electron transfer agent phosphate derivative; (b) at leas tone di-electron transfer agent phosphate derivative; wherein the amount of mono-electron transfer agent phosphate derivatives is no less than equimolar to the amount of di-electron transfer agent phosphate; and (c) a suitable carrier.

BNSDOCID: <WO___0240033A1_I_>

Formulation Containing Phosphate Derivatives of Electron Transfer Agents

Field of the invention

The invention relates to a therapeutic formulation containing phosphate derivatives of electron transfer agents. More particularly, this invention relates to a therapeutic formulation containing mono-electron transfer agent phosphate derivatives and di-electron transfer agent phosphate derivatives.

The invention also relates to a detergent composition containing surface active agents.

Background of the invention

In this specification, where a document, act or item of knowledge is referred to or discussed, this reference or discussion is not to be taken as an admission that the document, act or item of knowledge or any combination thereof was at the priority date:

(a) part of common general knowledge; or

(b) known to be relevant to an attempt to solve any problem with which this specification is concerned.

Whilst the following discussion concerns tocopherol and dermal therapy, it is also to be understood that the same principles apply to any application in which a therapeutic formulation containing electron transfer agents may be used.

The skin is the largest organ of the body, and, among other things, functions to protect the internal organs from external chemical, physical and pathological hazards. Normal skin is composed of an outer epidermis covering sub dermal layers, where each layer comprises different sections. The outer cornified layer of the epidermis possesses properties of strength, flexibility, high electrical impedance and dryness that retards penetration and proliferation of microorganisms. The cornified protective layer is formed by the migration of maturing keratinocytes that are formed at the junction of the dermis and epidermis.

Vitamin E (tocopherol) is an essential part of skin dynamics and is known to be very important for skin health, with deficiency manifesting as a cornified, scaly delicate skin, thickened epidermis, scaling, lesions, chronic infection, inflammation and erythema. Vitamin E is the main naturally occurring lipid soluble agent protecting the skin from stress, and is the main lipid soluble agent protecting the cell membrane lipids from peroxidation.

Skin is subject to constant stress due to exposure to everyday elements – sun, wind and water. As a result, it is common for many topical personal care products such as lotions, moisturizers, shampoo and conditioners to contain vitamin E in various forms to assist in maintaining skin health. In order to assist in maintaining skin health, it is necessary for the vitamin E to reach the target area of the dermis. The most direct method of achieving this targeting is to apply a topical formulation to the affected area. However, topical application of vitamin E to the skin using current formulations has variable success due to the skin's ability to erect an impenetrable barrier to many outside elements. It is critical to provide for the penetration of vitamin E through the epidermis to the dermis.

The use of free tocopherol is avoided because it is unstable, therefore suitable derivatives must be found. In the alimentary canal, it has been found that there is lipase activity which releases free tocopherol from the esters of tocopherol, typically the acetate ester. This lipase activity enables the use of tocopheryl acetate as a nutritional source of Vitamin E.

In contrast, the surface of the skin is deficient in lipase activity unless it is infected with microorganisms that are able to digest sebaceous excretions. Thus tocopheryl acetate must first diffuse through the epidermis into the vital derma, where the cells have a very limited lipase activity which releases the Vitamin E. It is believed that topical formulations using tocopherol acetate have not been able to deliver adequate tocopherol beyond the epidermal layers, and therefore provide little benefit. Since tocopheryl acetate is a lipidic material requiring formulation with an oil in water emulsion, absorption from such a formulation is less than optimal.

The epidermis is permeable to water soluble substances, such as tocopheryl phosphate. Until now producers of formulations containing tocopheryl phosphate utilized mono-tocopheryl phosphate isolated from the mixture produced during phosphorylation. The phosphorylation has been typically achieved using phosphorous oxychloride. The product was purified because it was believed that the by-products were deleterious to the efficacy of the mono-tocopheryl phosphate because not all the by-products were water soluble. The perceived deleterious effects were considered significant enough to justify the cost of complicated purification processes. Typically, the purification is performed by using ethanol to extract the di-tocopheryl phosphate and free tocopherol by-products.

Summary of the Invention

It has been found that the use of a non-purified or semi-purified electron transfer agent phosphorylation therapeutic product is efficacious. In particular, the non-water soluble di-electron transfer agent phosphate derivatives do not have a deleterious effect on the efficacy of the therapeutic product and may even provide a synergistic effect which results in beneficial properties which enhance the dermal penetration and/or efficacy of the mono-electron transfer agent phosphate derivatives.

According to a first aspect of the invention, there is provided an emulsion composition for therapeutic administration comprising the following:

(a) at least one mono-electron transfer agent phosphate derivative;

(b) at least one di-electron transfer agent phosphate derivative;

wherein the amount of mono-electron transfer agent phosphate derivative is no less than equimolar to the amount of di-electron transfer agent phosphate derivative; and

(c) a suitable carrier.

According to a second aspect of the invention, there is provided a method for administering to a subject electron transfer agent phosphate derivatives comprising the step of administering an emulsion composition comprising the following:

(a) at least one mono-electron transfer agent phosphate derivative;

(b) at least one di-electron transfer agent phosphate derivative;

wherein the amount of mono-electron transfer agent phosphate derivative is no less than equimolar to the amount of di-electron transfer agent phosphate derivative; and

(c) a suitable carrier.

The term "electron transfer agent" is used herein to refer to the class of chemicals which may be phosphorylated and which (in the non-phosphorylated form) can accept an electron to generate a relatively stable molecular radical or accept two electrons to allow the compound to participate in a reversible redox system. Examples of classes of electron transfer agent compounds that may be phosphorylated include hydroxy chromans including alpha, beta and gamma tocopherol, tocols and tocotrienols in enantiomeric and raecemic forms; quinols being

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the reduced forms of vitamin K1 and ubiquinone; hydroxy carotenoids including retinol; and ascorbic acid.

The phosphate derivatives of electron transfer agents comprise compounds covalently bound by means of an oxygen to the phosphorus atom of a phosphate group. The oxygen atom is typically derived from a hydroxyl group on the electron transfer agents. The phosphate derivative may exist in the form of a free phosphate acid, a salt thereof, a di-phosphate ester thereby including two molecules of electron transfer agent, a mixed ester including two different compounds selected from electron transfer agents, a phosphatidyl compound wherein the free phosphate oxygen forms a bond with an alkyl or substituted alkyl group, or a complex with a complexing agent selected from amphoteric surfactant, cationic surfactant, amino acids having nitrogen functional groups or proteins rich in these amino acids..

Examples of acceptable salts of mono-tocopherol phosphate derivatives are selected from the group consisting of the di-sodium, di-potassium, di-lithium, di magnesium, mono-sodium, mono-potassium, mono-lithium, or mono-magnesium salts or mixtures thereof. Preferably, the acceptable salts of di-tocopheryl phosphate derivatives are selected from the sodium, potassium, lithium or magnesium salts. The di-tocopheryl phosphate derivatives will usually only form a salt in the environment required to form the di-metal salts of mono-tocopheryl phosphate derivatives.

Preferably, the molar ratio of mono-electron transfer agent phosphate derivatives to di-electron transfer agent phosphate derivatives is in the range from 85:15 to 65:35. There must be enough di-electron transfer agent phosphate derivatives to form an emulsion and prevent the mono-electron transfer agent phosphate derivatives from going completely into solution, but not so much di-electron transfer agent phosphate derivatives that there is precipitation.

The mixture of mono-electron transfer agent phosphate derivatives and di-electron transfer agent phosphate derivatives can be prepared by recombining the purified individual components or by using the unpurified or semi-purified reaction product of a phosphorylation process. Preferably, the mixture is obtained by using the reaction product of a phosphorylation process. The source of a mixture of tocopheryl phosphate derivatives is preferably the reaction product of the phosphorylation of tocopherol using P_4O_{10}.

The term "acceptable carrier" is used herein to refer to a carrier considered by those skilled in the drug, food or cosmetic arts to be non-toxic when used to treat humans, animals or plant in parenteral or enteral formulations. The carrier chosen will depend on the route of

administration. Ingestible formulations includes tablets, capsules, powders, chewable tablets, capsules, oral suspensions, children's formulations, enteral feeds, nutraceuticals and functional foods. For a topical application, the carrier typically comprises hydrophilic substances such as water, glycerol, polyethyleneglycol, sorbitol or propanol. For example, the composition could be used as a shampoo, hair conditioner, moisturizing cream or lotion or lipstick as a topical application.

According to a third aspect of the invention, there is a process for preparing a therapeutic formulation containing phosphate derivatives of electron transfer agents comprising the steps of:

(a) phosphorylating one or more electron transfer agents using P_4O_{10} to form a mixture of at least one mono-electron transfer agent phosphate derivative and at least one di-electron transfer agent phosphate derivative;

wherein the amount of mono-electron transfer agent phosphate derivative is no less than equimolar to the amount of di-electron transfer agent phosphate derivative; and

(b) combining the mixture of mono-electron transfer agent phosphate derivative and di-electron transfer agent phosphate derivative with a suitable carrier.

The mono-electron transfer agent phosphate derivatives have good water solubility, therefore before they can be absorbed into the skin or hair an aqueous topically applied composition must dry. In contrast, di-electron transfer agent phosphate derivatives are not water soluble and cause the formation of an unstable emulsion when emulsified with water and other hydrophilic solvents. Without wishing to be bound by theory, it is noted that skin is hydrophobic so when the composition is spread onto the skin, the droplets in the emulsion are attracted to the skin. The micelles become unstable near a hydrophobic surface and break so the mono-electron transfer agent phosphate derivatives are released onto the skin. The mono-electron transfer agent phosphate derivatives can then diffuse through the epidermis into the derma. Therefore, di-electron transfer agent phosphate derivatives (once considered a nuisance by-product) function as an effective spreading agent for the mono-electron transfer agent phosphate derivatives.

Again, without wishing to be bound by theory, it is considered necessary for a product which is being ingested to have several types of surface activity including detergency and appropriate surface tension to facilitate absorption. Mono-electron transfer agent phosphate derivatives

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may have strong detergency but do not have sufficient surface tension effects. Therefore, the mixture of mono-electron transfer agent phosphate derivatives and di-electron transfer agent phosphate derivatives having self-emulsification properties which include both types of surface activity, that is, strong detergency and strong surface tensions, will be better absorbed, especially in the small intestine.

It has surprisingly further been found that pure mono-tocopheryl phosphate and its salts are powerful surface active agents and detergents giving a stable foam.

According to a fourth aspect of the invention, there is provided a detergent composition comprising a surface active agent selected from the group consisting of mono-tocopheryl phosphate, its salts and mixtures thereof.

There is also provided a method of increasing the surface activity and detergency of a composition by adding a surface active agent selected from the group consisting of mono-tocopheryl phosphate, its salts and mixtures thereof.

Again, whilst not wishing to be bound by theory, it is thought that this detergent property may be due to the fact that mono-tocopheryl phosphate is in the form of a polar head and a non-polar tail. In contrast, di-tocopheryl phosphate has 2 non-polar tails and a polar central group which makes it surface active but it is not a detergent because at high concentrations it accumulates in the surface layer of the composition and acts as a foam breaker because the surface becomes predominantly non-polar.

Examples

The invention will now be further illustrated and explained by reference to the following non-limiting examples.

Example 1

In this example, a therapeutic formulation according to the invention was prepared using tocopherol as the electron transfer agent.

Preparation of the tocopheryl phosphate mixture

Take 500 g dl-alpha-tocopherol and mix with a high shear mixer 4 aliquots each of 21g of P_4O_{10} at 12 minute intervals, holding the temperature above 60°C. While the mixture is still hot, add over 1.5 hours 91.5 g of sodium hydroxide which has been dissolved in 62.5 g of water at 50°C to hydrolyse and neutralise the tocopheryl phosphates. The product was cooled

to ambient temperature then further cooled with liquid nitrogen to give a brittle product that was ground to a powder and dried under vacuum.

The mole ratio of mono-tocopheryl phosphate to di-tocopheryl phosphate was approximately 70:30. The product contained mono and di sodium tocopheryl phosphate (approx. 65-85% by mole), sodium di-tocopheryl phosphate (approx. 10-35% by mole) and some sodium di-tocopheryl pyrophosphate.

Preparation and application of the topical formulation

The dried powder was dispersed in water as a 5% solution. 10 ml of this solution was applied to the hands to give a satisfactory application of the tocopheryl phosphates to the skin.

Example 2

The skin penetration properties of a mixture of mono- and di-tocopheryl phosphates according to the invention were compared to tocopheryl acetate.

Test formulations

The test materials are made up on the basis of 5% mixed actives (mono-tocopheryl phosphate (TP), di-tocopheryl phosphate (T2P) or tocopheryl acetate) in a vehicle consisting of 95/5 distilled water/ethanol with pH adjusted (if necessary to 6.5-7.0 with citric acid or dilute NaOH).

TP and T2P (mixed sodium salts)

A slurry of 6.25 w/w % of 80% mixed TP and T2P in 93.75 w/w % of the 95/5-water/ethanol mixture was prepared.

Active	TP & T2P (micrograms per applied dose)
tocopheryl phosphate	252
di-tocopheryl phosphate	1194
tocopherol	24

TP and T2P complexed

The TPC used was lauryl-imino di-propionic acid tocopheryl phosphate, a surface-active amphoteric phosphate ester complex formed from lauryl imino propionic acid (Deriphat 160) and tocopheryl phosphates. The solution was based on 40% active mixed phosphates as the latter is reacted/combined in a 60/40-amphoteric/mixed-phosphate weight ratio (1.9-1 mole ratio). 12.5 w/w % of the complex was dissolved in 87.5 w/w % of 95/5 water/ethanol mixture.

Active	TP and T2P complexed (micrograms per applied dose)
tocopheryl phosphate	188
di-tocopheryl phosphate	713
Tocopherol	20

Tocopheryl Acetate

Tocopheryl acetate is obtained from Roche/BASF. 5.0 w/w % of tocopheryl acetate was dispersed in 95.0 w/w % of 95/5 water/ethanol mixture.

Method

The test formulations are evaluated in *in vitro* human skin penetration studies. Samples are analyzed for the mono- and di-tocopheryl phosphates, free alpha-tocopherol, and tocopheryl acetate by high performance liquid chromatography (HPLC). The tests are conducted by DermTech International (San Diego, CA). Human cadaver skin samples are obtained and prepared. Each formulation is evaluated on triplicate sections from each donor at a topically applied dose of 5 $\mu L/cm^2$. Receptor solutions are collected over 48 hours at pre-selected time intervals. After 48 hours the skin surface is washed with isopropyl alcohol, and the skin is collected and split into epidermis and dermis. The skin sections are extracted with isopropyl alcohol. All collected samples are processed and assayed for tocopherol, tocopheryl acetate, tocopheryl phosphate and di-tocopheryl phosphate.

Mass balance from the samples is between 80-120% of the applied dose.

No tocopherols are observed in the receptor solution. This could be a result of amounts being below limits of detection, or degradation of the various tocopherol species into other, as yet uncharacterized, compounds.

TABLE 1 :SKIN PENETRATION STUDY

(Percent Distribution of Tocopherols Recovered; wt/wt %).

Treatment	α-Tocopherol	TP	T_2P
TP & T2P (mixed sodium salts)			
Surface wash	65.05	41.40	56.05
Epidermis	26.74	47.06	37.31
Dermis	8.24	11.42	6.62
Dermis/Epidermis Ratio	0.31	0.24	0.18
TP & T2P complexed			
Surface wash	50.00	48.82	70.92
Epidermis	35.99	24.55	16.67
Dermis	14.07	26.62	12.36
Dermis/Epidermis Ratio	0.39	1.08	0.74
Tocopherol Acetate	**α-Tocopherol**	—	—
Surface wash	91.48		
Epidermis	7.13		
Dermis	1.39		
Dermis/Epidermis Ratio	0.20		

Conclusions

The results demonstrate that the inclusion of 20 to 30% of T2P in the formulation did not have a deleterious effect on the performance of the tocopheryl phosphate product. Further, both of the TP/T2P mixtures were more efficiently transported into the dermis than the tocopheryl acetate product.

Example 3

In this example, a mixture was prepared comprising mono-ubiquinyl phosphate and di-ubiquinyl phosphate made according to the invention.

100g of ubiquinone was partially dissolved in 200ml of hot glacial acetic acid. To the vigorously stirred solution, small amounts of zinc (total of 30g) were added until the solution changed from yellow to green and then became colorless. The hot solution was filtered and the unreacted zinc was washed 2 more times (50ml) with hot glacial acetic acid to recover any remaining ubiquinol. Glacial acetic acid was removed from the ubiquinol by vacuum distillation or by cooling the solution to 0°C and filtering off the crystallized ubiquinol. To further remove any traces of acetic acid, the ubiquinol was placed under high vacuum (1mm Hg) for a period of 2 hours.

The ubiquinol product was treated immediately by heating to 100°C and adding 33g of P_4O_{10}. The mixture was stirred for 3 hours and then 500 ml water was introduced slowly into the mixture. The temperature of the reaction was maintained just below boiling point for a further 1 hour. Removal of water yielded ubiquinyl phosphates and phosphoric acid. The phosphoric acid was partially removed by further washes with hot water.

The final product consisted of 139g of mono-ubiquinyl phosphate, di-ubiquinyl phosphate and phosphoric acid. The product was analyzed by ^{31}P NMR and the molar ratio of mono-ubiquinyl phosphate : di-ubiquinyl phosphate was 76:24.

Example 4

In this example, the surface active properties of mono-tocopheryl phosphate was investigated.

0.1 g of pure di-sodium mono-tocopheryl phosphate was dissolved in 10 ml of pure distilled water in a 50 ml cylindrical stoppered vessel. The vessel was shaken on a test tube agitator and the headspace filled with stable foam. The foam was examined on a daily basis and showed complete stability for one day and then slowly degraded over the rest of the four-day period.

Mono-tocopheryl phosphate is therefore a surface active agent with detergent properties.

The word 'comprising' and forms of the word 'comprising' as used in this description and in the claims does not limit the invention claimed to exclude any variants or additions.

Modifications and improvements to the invention will be readily apparent to those skilled in the art. Such modifications and improvements are intended to be within the scope of this invention.

WHAT IS CLAIMED IS:

1. An emulsion composition for therapeutic administration comprising:

(a) at least one mono-electron transfer agent phosphate derivative;

(b) at least one di-electron transfer agent phosphate derivative;

wherein the amount of mono-electron transfer agent phosphate derivative is no less than equimolar to the amount of di-electron transfer agent phosphate derivative; and

(c) a suitable carrier.

2. A composition according to claim 1 wherein the molar ratio of mono-electron transfer agent phosphate derivative to di-electron transfer agent phosphate derivative is in the range from 85:15 to 65:35.

3. A composition according to claim 1 wherein the mono-electron transfer agent phosphate derivative and the di-electron transfer agent phosphate derivative are derived from alpha-tocopherol.

4. A composition according to claim 1 wherein the mono-electron transfer agent phosphate derivative and the di-electron transfer agent phosphate derivative are complexed with a complexing reagent selected from amphoteric surfactants, cationic surfactants, amino acids having nitrogen functional groups and proteins rich in these amino acids.

5. A method for administering to a subject phosphate derivatives of electron transfer agent comprising the step of administering an emulsion composition comprising the following:

(a) at least one mono-electron transfer agent phosphate derivative;

(b) at least one di-electron transfer agent phosphate derivative;

wherein the amount of mono-electron transfer agent phosphate derivative is no less than equimolar to the amount of di-electron transfer agent phosphate derivative; and

(c) a suitable carrier.

6. A process for preparing a therapeutic formulation containing phosphate derivatives of electron transfer agents comprising the steps of:

(a) phosphorylating one or more electron transfer agents using P_4O_{10} to form a mixture of at least one mono-electron transfer agent phosphate derivative and at least one di-electron transfer agent phosphate derivative;

wherein the amount of mono-electron transfer agent phosphate derivative is no less than equimolar to the amount of di-electron transfer agent phosphate derivative; and

(b) combining the mixture of mono-electron transfer agent phosphate derivative and di-electron transfer agent phosphate derivative with a suitable carrier.

7. An emulsion composition for topical application comprising:

(a) at least one mono-tocopheryl phosphate derivative;

(b) at least one di-tocopheryl phosphate derivative;

wherein the amount of mono-tocopheryl phosphate derivative is no less than equimolar to the amount of a di-tocopheryl phosphate derivative; and

(c) a suitable carrier.

8. A composition comprising a surface active agent selected from the group consisting of mono-tocopheryl phosphate, its salts and mixtures thereof.

9. A method of increasing the surface activity and detergency of a composition by adding a surface active agent selected from the group consisting of mono-tocopheryl phosphate, its salts and mixtures thereof.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01475

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[7]: A61K 31/662, 9/107, A61P 17/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC AS ABOVE

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT, CAPLUS: Tocopheryl phosphate, tocopherol phosphate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6046181A (OONISHI et al.). 4 April 2000 Abstract, Col.15 lines 50-63, Example B-1, Example B-2, Example B-10, Example B-11, Example B-15, Example B-23* and Example B-24	1-9

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" Document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 December 2001	- 3 JAN 2002
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No.: (02) 6285 3929	Authorized officer STEVEN CHEW Telephone No.: (02) 6283 2248

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU01/01475

Box 1 Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,2,4-6
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The claims are so broad in scope that a complete search is not possible. Claims 1,2,4,5 and 6 relate to a composition comprising at least one mono-electron transfer agent phosphate derivative and at least one di-electron transfer agent phosphate derivative. The claims cover a very broad range of compounds where as the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case a complete search over the whole of the claimed scope is not feasible. Consequently the search has been carried out for those parts of the claims which appear to be supported and disclosed such as the examples disclosed in the description with due regards to the general idea underlying the application.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

PNEDOCID: <WO 0240033A1 I >

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01475

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5387579A (MEYBECK et al.) 7 February 1995 Abstract and Examples	8
X	Derwnt Abstract Accession No. 98-071819/07. Class B02 D21, JP 0930813A (NONO GAWA SHOJI KK) 2 December 1997 Abstract	8
A	STN File CA, Abstract 111:45280, + JP 1986-2817293 (SHISEIDO CO. LTD et al.), 2 December 1986 Abstract	1-9

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU01/01475

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	6046181	CN	1173869	EP	798305	US	5965750
		WO	9714705				
US	5387579	CA	2075201	EP	513104	EP	652010
		FR	2657526	US	5656618	US	5952001
		WO	9111189				

END OF ANNEX

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